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We Claim:

1. A heterologous fusion protein comprising a GLP-1 analog comprising a sequence selected from the group consisting of:

- a) (SEQ ID NO:1)

5 His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly

wherein Xaa₈ is selected from Gly and Val;

- b) (SEQ ID NO:2)

10 His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Gly

wherein Xaa₈ is selected from Gly and Val;

- c) (SEQ ID NO:3)

15 His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Pro

wherein Xaa₈ is selected from Gly and Val;

- d) (SEQ ID NO:4)

20 His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Pro

wherein Xaa₈ is selected from Gly and Val;

- e) (SEQ ID NO:5)

His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly

wherein Xaa₈ is selected from Gly and Val;

- f) (SEQ ID NO:6)

25 His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly

wherein Xaa₈ is selected from Gly and Val;

fused to the Fc portion of an immunoglobulin comprising the sequence of SEQ ID
NO:7

30 Ala-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-
Xaa₁₆-Xaa₁₇-Xaa₁₈-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-
Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-

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Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-
 Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-
 Glu-Glu-Gln-Phe-Xaa₈₀-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-
 Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-
 5 Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-
 Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-
 Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-
 Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-
 Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-
 10 Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-
 Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-
 Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-
 Leu-Ser-Leu-Gly-Xaa₂₃₀ (SEQ ID NO:7)

wherein:

15 Xaa at position 16 is Pro or Glu;
 Xaa at position 17 is Phe, Val, or Ala;
 Xaa at position 18 is Leu, Glu, or Ala;
 Xaa at position 80 is Asn or Ala; and
 Xaa at position 230 is Lys or is absent.

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2. The heterologous fusion protein of Claim 1 wherein the C-terminal glycine residue of the GLP-1 analog is fused to the N-terminal alanine residue of the Fc portion via a peptide linker comprising a sequence selected from the group consisting of:
- 25
- a) Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:8);
- b) Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:19); and
- 30
- c) Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser-Gly-Gly-Gly-Gly-Ser (SEQ ID NO:21).
3. The heterologous fusion protein of Claim 2 wherein the linker comprises the sequence of SEQ ID NO:8.

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4. The heterologous fusion protein of any one of Claims 1 to 3 wherein Xaa at position 8 of the GLP-1 analog is Gly.
5. The heterologous fusion protein of any one of Claims 1 to 3 wherein Xaa at position 8 of the GLP-1 analog is Val.
- 5 6. The heterologous fusion protein of any one of Claims 1 to 3 wherein the GLP-1 analog comprises the sequence of SEQ ID NO:1.
7. A heterologous fusion protein selected from the group consisting of: a) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P); b) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A); c) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, N297A); d) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A, N297A); e) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P); f) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A); g) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, N297A); h) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A, N297A); i) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P); j) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A); k) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, N297A); l) Gly⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A, N297A); and the des-K forms thereof.
- 10 8. A heterologous fusion protein selected from the group consisting of: a) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P); b) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A); c) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, N297A); d) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1L-IgG4 (S228P, F234A, L235A, N297A); e) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P); f) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A); g) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, N297A); h) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-1.5L-IgG4 (S228P, F234A, L235A, N297A); i) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P); j) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A); k) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, N297A); l) Val⁸-Glu²²-Gly³⁶-GLP-1(7-37)-2L-IgG4 (S228P, F234A, L235A, N297A); and the des-K forms thereof.
- 20 9. A polynucleotide encoding the heterologous fusion protein of any one of Claims 1 to 8.
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10. A vector comprising the polynucleotide of Claim 9.
11. A host cell comprising the vector of Claim 10.
12. A host cell expressing at least one heterologous fusion protein of any one of Claims 1 to 8.
- 5 13. The host cell of Claim 12 wherein the host cell is a CHO cell.
14. The host cell of Claim 12 wherein the host cell is a NS0 cell.
15. A process for producing a heterologous fusion protein comprising the steps of transcribing and translating a polynucleotide of Claim 9 under conditions wherein the heterologous fusion protein is expressed in detectable amounts.
- 10 16. A method of treating a patient with non-insulin dependent diabetes mellitus comprising the administration of a therapeutically effective amount of the heterologous fusion protein of any one of Claims 1 to 8.
17. A method of inducing weight loss in an overweight patient comprising the administrations of a therapeutically effective amount of the heterologous fusion
- 15 protein of any one of Claims 1 to 8.
18. The method of Claim 16 or 17 wherein the heterologous fusion protein is administered at a dose between about 0.05 mg/kg to 0.5 mg/kg body weight.
19. The method of Claim 16 or 17 wherein the heterologous fusion protein is administered once a week.
- 20 20. Use of the heterologous fusion protein of any one of Claims 1 to 8 for use as a medicament.
21. Use of the heterologous fusion protein of any one of Claims 1 to 8 for the manufacture of a medicament to treat non-insulin dependent diabetes mellitus.
22. Use of the heterologous fusion protein of any one of Claims 1 to 8 for the
- 25 manufacture of a medicament to treat obesity or induce weight loss in an overweight subject.
23. Use of the heterologous fusion protein of any one of Claims 1 to 8 for the treatment of a human or animal body by therapy.

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24. A heterologous fusion protein comprising a GLP-1 analog comprising a sequence selected from the group consisting of:

a) (SEQ ID NO:1)

His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Gly

wherein Xaa₈ is selected from Gly and Val;

b) (SEQ ID NO:2)

His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Gly

wherein Xaa₈ is selected from Gly and Val;

c) (SEQ ID NO:3)

His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly-Pro

wherein Xaa₈ is selected from Gly and Val;

d) (SEQ ID NO:4)

His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly-Pro

wherein Xaa₈ is selected from Gly and Val;

e) (SEQ ID NO:5)

His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Gly

wherein Xaa₈ is selected from Gly and Val;

f) (SEQ ID NO:6)

His-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Glu-
Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Lys-Asn-Gly-Gly

wherein Xaa₈ is selected from Gly and Val;

fused to the Fc portion of an immunoglobulin comprising the sequence of SEQ ID NO:7

Ala₁-Glu-Ser-Lys-Tyr-Gly-Pro-Pro-Cys-Pro-Pro-Cys-Pro-Ala-Pro-
Xaa₁₆-Xaa₁₇-Xaa₁₈-Gly-Gly-Pro-Ser-Val-Phe-Leu-Phe-Pro-Pro-Lys-Pro-
Lys-Asp-Thr-Leu-Met-Ile-Ser-Arg-Thr-Pro-Glu-Val-Thr-Cys-Val-
Val-Val-Asp-Val-Ser-Gln-Glu-Asp-Pro-Glu-Val-Gln-Phe-Asn-Trp-

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Tyr-Val-Asp-Gly-Val-Glu-Val-His-Asn-Ala-Lys-Thr-Lys-Pro-Arg-
Glu-Glu-Gln-Phe-Xaa₈₀-Ser-Thr-Tyr-Arg-Val-Val-Ser-Val-Leu-Thr-
Val-Leu-His-Gln-Asp-Trp-Leu-Asn-Gly-Lys-Glu-Tyr-Lys-Cys-Lys-
Val-Ser-Asn-Lys-Gly-Leu-Pro-Ser-Ser-Ile-Glu-Lys-Thr-Ile-Ser-
5 Lys-Ala-Lys-Gly-Gln-Pro-Arg-Glu-Pro-Gln-Val-Tyr-Thr-Leu-Pro-
Pro-Ser-Gln-Glu-Glu-Met-Thr-Lys-Asn-Gln-Val-Ser-Leu-Thr-Cys-
Leu-Val-Lys-Gly-Phe-Tyr-Pro-Ser-Asp-Ile-Ala-Val-Glu-Trp-Glu-
Ser-Asn-Gly-Gln-Pro-Glu-Asn-Asn-Tyr-Lys-Thr-Thr-Pro-Pro-Val-
Leu-Asp-Ser-Asp-Gly-Ser-Phe-Phe-Leu-Tyr-Ser-Arg-Leu-Thr-Val-
10 Asp-Lys-Ser-Arg-Trp-Gln-Glu-Gly-Asn-Val-Phe-Ser-Cys-Ser-Val-
Met-His-Glu-Ala-Leu-His-Asn-His-Tyr-Thr-Gln-Lys-Ser-Leu-Ser-
Leu-Ser-Leu-Gly-Xaa₂₃₀ (SEQ ID NO:7)

wherein:

Ala at position 1 is absent;
15 Xaa at position 16 is Pro or Glu;
Xaa at position 17 is Phe, Val, or Ala;
Xaa at position 18 is Leu, Glu, or Ala;
Xaa at position 80 is Asn or Ala; and
20 Xaa at position 230 is Lys or is absent.